

a.) Amendment to the Specification

Please amend the paragraphs starting at page 112, line 12 and ending at page 116, line 11 to read as follows.

Fig-3 Fig. 3A-B shows the specific reactivity of anti-hIGF CDR-grafted antibody for hIGF-I (binding ELISA). The abscissa shows antibody concentration, and the ordinate shows binding activity as absorbance (415 nm). Fig. 3a shows the results of the anti-hIGF human chimeric antibody KM3002 as expressed in □; the results of the anti-hIGF CDR-grafted antibody CamHV0/LV0 as expressed in ○; the results of the anti-hIGF CDR-grafted antibody QAR/LV0 as expressed in △; the results of the anti-hIGF CDR-grafted antibody QGAR/LV0 as expressed in ■; and the results of the anti-hIGF CDR-grafted antibody CamHV0/NYPLL3A11 as expressed in ●, respectively; and Fig.3b shows the results of the anti-hIGF human chimeric antibody KM3002 as expressed in □; the results of the anti-hIGF CDR-grafted antibody CamHV0/LV0 as expressed in ○; the results of the anti-hIGF CDR-grafted antibody QGAR/LV0 as expressed in ◇; the results of the anti-hIGF CDR-grafted antibody QGAR/NYPLL3A11 as expressed in △; the results of the anti-hIGF CDR-grafted antibody QGAR/PLDFT as expressed in ●; and the results of the anti-hIGF CDR-grafted antibody QGAR/PLLDFT as expressed in ■, respectively.

Fig.4 Fig. 4A-B shows the hIGF-I- or hIGF-II-dependent cell proliferation inhibitory effect of anti-hIGF CDR-grafted antibody. Fig.4a shows the results in the presence of 10 ng/ml hIGF-I, and Fig.4b shows the results in the presence of 20 ng/ml hIGF-II, respectively. The abscissa shows antibody concentration (μg/ml), and the ordinate shows the value of cell proliferation as absorbance (OD450 nm), respectively. In

the drawings, solid line shows the baseline of cell proliferation in the presence of hIGF-I or hIGF-II and in the absence of antibody, and dotted line shows the baseline of cell proliferation in the absence of hIGF-I or hIGF-II and in the absence of antibody, respectively. The symbol □ shows the results of anti-hIGF human chimeric antibody KM3002; ○ shows the results of anti-hIGF CDR-grafted antibody CamHV0/LV0; △ shows the results of anti-hIGF CDR-grafted antibody QAR/LV0; and ■ shows the results of anti-hIGF CDR-grafted antibody QGAR/LV0, respectively.

Fig.5 Fig. 5A-B shows the hIGF-I- or hIGF-II-dependent cell proliferation inhibitory effect of anti-hIGF CDR-grafted antibody. Fig.5a shows the results in the presence of 10 ng/ml hIGF-I, and Fig.5b shows the results in the presence of 20 ng/ml hIGF-II, respectively. The abscissa shows antibody concentration (μg/ml), and the ordinate shows the value of cell proliferation as absorbance (OD450 nm), respectively. In the drawings, solid line shows the baseline of cell proliferation in the presence of hIGF-I or hIGF-II and in the absence of antibody, and dotted line shows the baseline of cell proliferation in the absence of hIGF-I or hIGF-II and in the absence of antibody, respectively. The symbol □ shows the results of anti-hIGF human chimeric antibody KM3002; ○ shows the results of anti-hIGF CDR-grafted antibody CamHV0/LV0; △ shows the results of anti-hIGF CDR-grafted antibody QGAR/LV0; ◇ shows the results of anti-hIGF CDR-grafted antibody CamHV0/NYPLL3A11; and ■ shows the results of anti-hIGF CDR-grafted antibody QGAR/NYPLL3A11, respectively.

Fig.6 Fig. 6A-B shows the hIGF-I- or hIGF-II-dependent cell proliferation inhibitory effect of anti-hIGF CDR-grafted antibody. Fig.6a shows the results in the presence of 10 ng/ml hIGF-I, and Fig.6b shows the results in the presence of 20 ng/ml

hIGF-II), respectively. The abscissa shows antibody concentration ($\mu\text{g/ml}$), and the ordinate shows the value of cell proliferation as absorbance (OD450 nm), respectively. In the drawings, solid line shows the baseline of cell proliferation in the presence of hIGF-I or hIGF-II and in the absence of antibody, and dotted line shows the baseline of cell proliferation in the absence of hIGF-I or hIGF-II and in the absence of antibody, respectively. The symbol \square shows the results of anti-hIGF human chimeric antibody KM3002; \diamond shows the results of anti-hIGF CDR-grafted antibody QGAR/LV0; \blacksquare shows the results of anti-hIGF CDR-grafted antibody QGAR/PLDFT; \bullet shows the results of anti-hIGF CDR-grafted antibody QGAR/PLLDFT; and \blacktriangle shows the results of anti-hIGF CDR-grafted antibody QGAR/NYPLL3A11, respectively.

Fig. 7 shows specific reactivity of anti-hIGF rat monoclonal antibody for hIGF-I (binding ELISA). In the graph, solid bar shows the results of methylated BSA-hIGF-I as an antigen, and blank bar shows the results of methylated BSA-BSA as an antigen.

Fig.8 shows reactivity of anti-hIGF rat monoclonal antibody for hIGF-I having authentic three-dimensional structure in a liquid system (competitive ELISA). The symbol \diamond shows the results with anti-hIGF rat monoclonal antibody KM1468; \blacksquare shows the results of anti-hIGF rat monoclonal antibody KM1470; \triangle shows the results of anti-hIGF rat monoclonal antibody KM1471; \times shows the results of anti-hIGF rat monoclonal antibody KM1472; and \circ shows the results of anti-hIGF rat monoclonal antibody KM1473, respectively.

Fig.9 Fig. 9A-B shows activity of various peptides to inhibit binding of anti-hIGF rat monoclonal antibody KM1468 to hIGF-I. The abscissa shows concentration

of each peptide ($\mu\text{g/ml}$), and the ordinate shows binding activity (%), respectively. Fig.9A shows the results of p1-18 as expressed in ●; the results of p24-35 as expressed in □; the results of p29-41 as expressed in ■; the results with p36-47 as expressed in △; the results of p61-70 as expressed in ◇; the results of p14-30 as expressed in ◆; and the results of p41-56 as expressed in ✕, respectively. Fig.9B shows the results of hIGF-I as expressed in ○; the results of p41-56C as expressed in ●; the results of p52-70 as expressed in □; the results of p1-18 and p41-56C as expressed in ■; the results of p1-18 and p52-70 as expressed in △; the results of p41-56C and p52-70 as expressed in ▲; and the results of p1-18, p41-56C and p52-70 as expressed in ◇, respectively.

Fig.10 Fig. 10A-B shows activities of hIGF-I, hIGF-II and human insulin to inhibit binding of anti-hIGF antibody KM1468 to hIGF-I and hIGF-II. Fig.10A shows inhibition by each factor upon binding of KM1468 to hIGF-I, and Fig.10B shows upon binding of KM1468 to hIGF-II. The abscissa shows concentration of respective factors ($\mu\text{g/ml}$), and the ordinate shows binding activity (%) wherein the value with no addition of factors is defined as 100%. The symbol ■ shows the results of hIGF-I; ○ shows the results of hIGF-II; and △ shows the results of human insulin, respectively.

Fig.11 shows the construction steps of plasmids pBS(II)SK(-)/hIGF-I and pKANTEX93/hIGF-I.

Fig.12 Fig. 12A-B shows the expression of hIGF-I in A549/hIGF-I cell. Fig.12A shows the inhibition by a recombinant hIGF-I protein. The abscissa shows the concentration of the added recombinant hIGF-I protein, and the ordinate shows the binding activity (OD415). Dotted line shows the results in the absence of the recombinant hIGF-I protein. Fig.12B shows hIGF-I contained in the culture supernatant of A549 cell and

A549/hIGF-I cell. Blank shows A549 cell, and mesh shows A549/hIGF-I cell, respectively.